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REMARKS

Claims 1, 4, 6-8, 10-14 and 19 are pending in the application. All claims stand rejected.

The only outstanding issue in this case is whether the claims are patentable over the teachings of JP '279 in view of JP '882.

The claims are directed to a drug composition comprising lecithin-modified superoxide dismutase (PC-SOD) and sucrose. Sucrose is added to the composition to stabilize the PC-SOD against degradation of the lecithin moieties.

The Examiner has taken the position that it would have been obvious to add sucrose to a PC-SOD composition in view of the prior art which teaches the addition of sucrose to SOD compositions in order "to avoid denaturation which occurs during the process of freeze-drying SOD."

None of the prior art references teach or suggest that either human PC-SOD or human SOD undergo denaturation during a freeze-drying process. As admitted by the Examiner, "JP '279 does not describe any stability problems with PC-SOD." Further, JP '882, rather than teaching that denaturation during freeze-drying is a problem, teaches that "No decreases in the enzymatic action of human SOD is observed when this protein is subjected to freezing and thawing or freeze-drying processes, nor is formation of insoluble matter visible to the naked eye." Thus, there is not any motivation for adding sucrose to a SOD composition in order to prevent denaturation and/or insolubility problems during freezing, thawing or freeze-drying of SOD. To the contrary, JP '882 discloses that the problem with SOD is that it forms undesirable dimers that could have allergenic side effects, and that the formation of dimers of SOD can be prevented by adding sugar alcohols, disaccharides and/or ketose monosaccharides.

The fact that JP '882 discloses that other stabilizers (e.g., albumin, DNA, etc.) have been used to prevent denaturation of different proteins is irrelevant. JP '882 teaches that the relevant problem with SOD is the formation of SOD dimers. There is not any known problem with dimerization of PC-SOD. PC-SOD is formed by binding four lecithin moieties to each SOD molecule. For those skilled in the art, it is easy to understand that the hydrophobic lecithin moieties create a large steric hindrance and cause repulsion of the PC-SOD molecules from each other, thereby preventing dimerization problems. Thus, there are significant

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differences between SOD and PC-SOD. SOD must be stabilized against dimerization, whereas dimerization is neither known nor expected with PC-SOD. To the contrary, the problem with PC-SOD is that the lecithin moieties tend to undergo degradation. Such degradation of lecithin moieties is not a factor with SOD.

Thus, the stability problem with PC-SOD is not at all a problem with SOD, since it does not have any lecithin moieties, and the stability problem with SOD (dimerization) is not a known or expected problem with PC-SOD. One skilled in the art would not expect a material that stabilizes a compound against dimerization to be useful for also solving a completely different and unrelated problem of preventing degradation of lecithin moieties.

From the Advisory Action and a prior telephonic interview with the Examiner, it is believed that the Examiner understands that the Applicants are using sucrose to solve an entirely different and unrelated stability problem (lecithin degradation rather than dimerization) on different substances (PC-SOD rather than SOD). However, the Examiner mistakenly believes that there is an alternative motive for using the stabilizers disclosed in the JP '882 reference on either SOD or PC-SOD. Specifically, the Examiner appears to believe that the JP '882 reference teaches that SOD is susceptible to denaturation upon freeze-drying. To the contrary, the JP '882 reference teaches that there is not any decrease in enzymatic activity of human SOD upon freezing, thawing or freeze-drying. The disclosure that other proteins undergo denaturation upon freeze-drying, and that such problems were previously overcome by employing "compounds such as albumin, DNA, carrageenan, dextran, or starch; amino acid; polyethylene glycol; or glycerol prior to freezing and thawing or freeze-drying" does not suggest that any of these materials would be useful for preventing dimerization of SOD, which from the JP '882 reference appears to be the only relevant problem with freeze-dried SOD.

There is not any suggestion in the prior that sucrose is useful for solving any problems with PC-SOD or SOD other than preventing dimerization, a problem that is not known to occur with PC-SOD. Nor is there any suggestion in the prior art that sucrose is useful for solving lecithin moiety degradation problems with PC-SOD, the only known stability problem with PC-SOD.

The fact that sucrose is useful for stabilizing PC-SOD against degradation of lecithin moieties and also useful for stabilizing SOD against dimerization is purely coincidental. There

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is not any known relationship between these problems, and one having ordinary skill in the art would not expect agents that are useful for stabilizing SOD against dimerization would also be useful for stabilizing the lecithin moieties of PC-SOD against degradation. In fact, among the numerous sugar alcohols, disaccharides, and ketose monosaccharides said to be useful for stabilizing SOD against dimerization, only sorbitol and sucrose were found to be useful for stabilizing PC-SOD against degradation of their lecithin moieties (see Table 2 at page 28 of the specification). However, sorbitol imparts an unacceptable paste-like property when lyophilized. Accordingly, the Applicants have discovered that only sucrose provides an acceptable stabilizing effect against degradation of the lecithin moieties of PC-SOD. This is not suggested by the prior art which only teaches that sucrose and various other materials may be employed to prevent dimerization of SOD, a different problem that is not known to occur with PC-SOD.

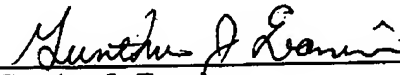
For these reasons, it is respectfully submitted that the rejections are based on errors of fact (i.e., that the prior art teaches the use of sucrose to prevent denaturation of SOD and/or PC-SOD), and that consideration of the actual facts compels withdrawal of the rejection. Therefore, a Notice of Allowance is requested.

Respectfully submitted,
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